PROPOSAL FOR TOPIC APPROVAL TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE DEGREE OF Ph.D. IN THE SUBJECT OF CHEMISTRY

Title of the Topic	Design and Green Synthesis of Some Solid-State Sulfonamide Active Pharmaceutical Ingredient Analogs
Name of the student	Ms. Amita Girish Mrunalini Dhadphale
Basic Qualification	M. Tech. Green Technology
In the case of Ph.D. student Year of passing GATE	2014
Name of Research supervisor/ Guide	Dr. Kamini Donde Professor Department of Chemistry, Ramnarain Ruia Autonomous College of Arts & Science
Date of superannuation/ retirement of the research supervisor/guide	31/03/2037
Name of research centre	Department of Chemistry, Ramnarain Ruia Autonomous College of Arts & Science
Signature of Student	ACDhadphale
Signature of Research supervisor/ Guide	
Date of submission of Research Proposal	24/06/2022

Seal of College

Principal
Ramnarain Ruia Autonomous College,
Matunga, Mumbai - 400 019.

Signature of Head/Director/
Principal Research centre

Index

Sr. No.	Content	Page No.
1	Title	3
2	Aim of the study	3
3	Objectives of study	3
4	Study Background (Literature Review) and significance of study	3
5	National status	5
6	International status	6
7	Study hypothesis	8
8	Study Rationale	8
9	Research Methodology	9
10	Statistical Plan	10
11	Limitations of the study	10
12	Expected Results and outcome	11
13	Select Bibliography	11

1. Title

Design and Green Synthesis of Some Solid-State Sulfonamide Active Pharmaceutical Ingredient Analogs

2. Aim of the study

The aim of study is to design and synthesize solid state analogs of sulfonamide APIs having improved physicochemical properties by green eco-friendly synthesis methods.

3. Objectives of study

- To design, synthesize and to characterize some sulfonamide analogs which would lead to increased understanding of the structure-property relationship.
- To promote modification and enhancement of physicochemical properties of selected potential APIs containing sulfonamide functional group in their structure in order to permit development of formulations with good solubility, dispersibility, stability, manufacturability, wettability, etc.
- To achieve improved physicochemical properties of potential sulfonamides by synthesis of solid-state analogs with green methods incorporating green chemistry principles.

4. Study Background (Literature Review) and significance of study

Solid state analogs such as amorphous and crystalline (polymorphs, co-crystals, salts, eutectic mixtures and solvates) of active pharmaceutical ingredients (APIs) have attracted many scientists, chemists and academicians as they show distinct physicochemical properties with respect to their parent solid state analogs. Some of these solid-state molecular modifications exhibit excellent improvement in solubility, thermal stability, chemical stability, dissolution rate, etc. [1]. Particularly, the phase change of polymorphic materials at different pressure and temperature is of fundamental interest in solid-state chemistry as they can exhibit different

physical and chemical properties for different crystal phases [2]. Synthesis and characterization of multi-component systems like co-crystals, eutectic mixtures, salts etc. exhibiting synergy or enhanced physicochemical properties or interactions with excipients or formulation inert is also area of interest in pre-formulation studies. The role of weak interactions and hydrogen bonds in the formation and determination of stable crystal structure of possible polymorphs, co-crystals etc. can be assessed by single crystal and powder X-ray diffraction methods [3]. The thermodynamic and kinetic relationship between the polymorphs can be established by thermal analysis and slurry methods [4].

Polymorphic crystals were exhibited in many organic compounds. The frequency changes, relative intensities, band contours, and number of bands were observed in the spectra of different polymorphism which may be due to molecule-molecule interactions in the crystal unit cells [5]. Organic compounds exhibit polymorphism and multicomponent systems formation due to the presence of functional groups, hydrogen bond donors and accepters, rotatable bonds etc. One of such functional group causing formation of single component as well as multicomponent systems is sulfonamide.

Sulfonamides are any member of a class of chemical compounds, the amides of sulfonic acids. The class includes several groups of drugs used in the treatment of bacterial infections, diabetes mellitus, oedema, hypertension, and gout. The bacteriostatic sulfonamide drugs, often called sulfa drugs, include sulfanilamide and numerous compounds closely related to it. Other groups of sulfonamide drugs have been developed by exploiting observations made during clinical evaluation of sulfanilamide derivatives. Examples of these drugs are probenecid, introduced as an agent for intensifying the action of penicillin but now principally used in treating gout; acetazolamide and furosemide, which are diuretics; and tolbutamide, a hypoglycaemic. Chlorothiazide and hydrochlorothiazide are effective both as diuretics and in reducing the blood pressure.

Many sulfonamide APIs are classified as Biopharmaceutics classification system (BCS) class II and class IV drugs (e.g. Furosemide: BCS Class IV, Celecoxib: BCS Class II) having low solubility issues and also have other stability issues such as hydration and polymorphic transformation etc. These problems can be addressed by formation suitable solid-state analogs of these sulfonamide APIs. Therefore, study of solid-state analogs of sulfonamide APIs becomes one of the most exciting areas of solid-state chemistry research that we would like to conduct.

There are various methods reported in the literature for synthesis of solid-state analogs of Sulfonamide APIs [6]. Gaining full control over phase transition and multi component system formation of crystalline APIs using various crystallization techniques like evaporative crystallization, high temperature crystallization, epitaxial crystallization, cooling crystallization etc. are widely reported in the literature [7]. These solvent-based crystallization methods require large volumes of solvents and can contribute to generation of hazardous waste. Some of these solvents leave traces of crystal lattice of API analogs which can promote further phase transition a can generate undesired polymorphs. Such mixtures then need to be purified which further increases the quantity of solvent and eventually generates hazardous waste.

Therefore, there is a need for greener approach to prepare solid state analogs of sulfonamides. The above research will prove helpful to develop eco-friendly synthesis methods that can be carried out under solvent free conditions or in the presence of minimal quantities of solvent and to establish the relation between at solid state molecular modifications and pharmaceutical requirements of determining the stability and interplay of these API analogs [8]. In this way this research is aimed to develop desirable single component and multi-component (including eutectic compositions) solid-state sulfonamide analogs based on pharmaceutical necessities by green synthesis methods.

5. National status

Solid form synthesis is a new area that includes polymorphs, cocrystal, salt, eutectics, solid solution, solvates and amorphous phases and it covers the various research topics of physical, organic, inorganic, metal-organic, supramolecular, computational, pharmaceutical, and solid material scientists in terms of synthesis and characterization [9,10,11]

The role of about 20 different solvents in the crystallization of polymorphs for 1,3- N-phenyl benzene sulphonamides was studied and five compounds were found to be dimorphic, and one was trimorphic. [12]

Multicomponent solid forms of the BCS class IV drug furosemide (FSM) were obtained upon liquid assisted grinding with conformers anthranilamide (ANT), 4-toluamide (TOL), 2-picolinamide (PCM), piperazine (PPZ), 2,3,5,6-tetramethylpyrazine (TMPZ), pyrazine (PYZ),

2-picolinic acid (PIC), isoniazid (INZ), and theophylline (THP), and identified with powder X-ray diffraction. [13]

The trimorphic cocrystals of celecoxib with δ-valerolactam contain sulphonamide dimers and catemers together with carboxamide dimers, whereas the caprolactam cocrystal is sustained by a SO2N–H···H–NOC heterosynthon. The alternation of synthons with even–odd ring coformers offered a crystal engineering approach to sulphonamide–carboxamide cocrystals [14].

6. International status

For organic molecular compounds the crystal form landscape is vast (Figure 1 and Figure 2). A compound as a single-component crystal can have polymorphs [15]. It can crystallize with solvent molecules to make hydrates or solvates [16]. It can also form other multi-component molecular crystals, i.e., cocrystals or salts, with compounds other than solvents. The cocrystals and salts can have hydrate or solvate forms and, in addition to this, all multi-component forms themselves can have polymorphs.

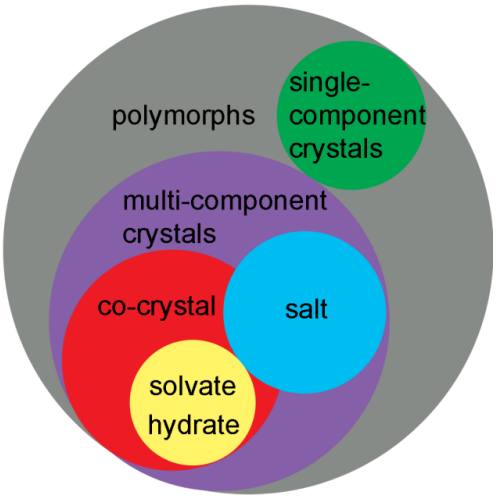

Figure 1: The crystal form landscape of molecular crystals

In this text, the following definitions will be used: Polymorphs are different crystal forms of species that have the same composition, i.e. different crystalline arrangements of one compound or two or more compounds with the same ratio. Cocrystals are multi-component molecular crystals, a group that also contains solvates. Cocrystals in this text refer mainly to crystals which contain compounds that are solids at standard conditions. Solvates are crystal

forms that have molecules of solvent in the crystal lattice, and these include hydrates as a special case in which the solvent is water.

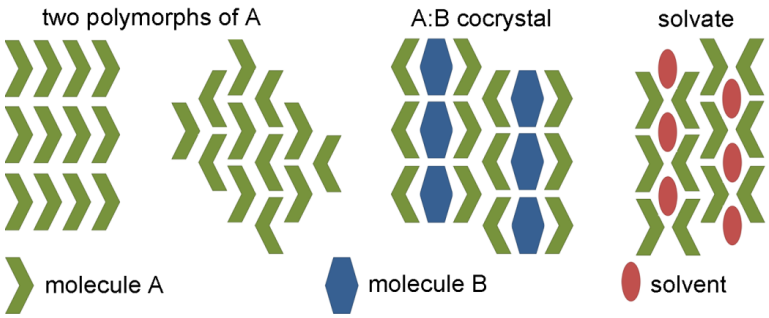

Figure 2: Some possible crystal forms of molecule A

Polymorphism in organic compounds is very often and of course fundamental importance since its ability to change the drug properties such as solubility, dissolution, toxicity and bioavailability for different crystal forms (Ritonavir: solubility order I > II and Mebendazole: order of toxicity effect B > A C) [17,18].

Sulfonamide APIs exhibit polymorphism as the p-amino group, the acidic Nl-hydrogen atom, and the oxygen of the S-O group are involved in intermolecular hydrogen bonding in molecular crystals of sulfonamides [19] there are various co-crystals of sulfonamide APIs various pharmaceutical actives and pharmaceutical excipients are also reported in the literature for e.g., Cobalt (II), Nickel (II), and Copper (II) derivatives of sulfacetamide [20], 1:1 co-crystal of sulfacetamide -caffeine [21], etc.

Green synthesis methods for preparation of co-crystals of APIs are also reported in the literature. Methods like solvent assisted grinding to reduce the quantity of solvent, hot melt extrusion, melt assisted grinding are used for bulk drug processing [22]. For example, green synthesis of Ibuprofen-Nicotinamide cocrystal by slurry method is reported [23]

Exact literature reference regarding green synthesis of solid-state sulfonamide analogs was not found in initial literature search. Hence, this can be the novel area for research.

7. Study hypothesis

This research project will test and prove the following hypothesis

Modification and improvement can be done in the physicochemical properties of Sulfonamide APIs belonging to BCS class II and IV by formation of solid-state analogs such as crystalline polymorphs, co-crystals, salts, eutectic mixtures and solvates.

Design and Synthesis of solid-state sulfonamide analogs is possible using green eco-friendly methods like solventless process, synthesis and crystallizations using the green solvents, water assisted synthesis of solid-state analogs, etc.

Characterization of these solid-state analogs prepared by green eco-friendly methods is also possible using various analytical tools like PXRD, DSC, IR, Solid State NMR, Single crystal X-ray Diffraction etc.

8. Study Rationale

Many potentially useful APIs with highly desirable molecular pharmacological properties may never realize their maximum potential because of the physical properties of the compound that display unfavourable bioavailability, unacceptable shelf life, difficulties in the formulation manufacturing, unacceptable thermal stability, hygroscopicity, low photo stability etc. In the recent years, there has been a steady increase in the number of low solubility compounds in the drug development. It is estimated that up to 90% of the new chemical entities would be categorized as BCS class II or IV compounds [24]. When comparing these numbers to that of marketed drugs where more than 50% are classified as highly soluble [25–27], it becomes evident that poor compound solubility is a major hurdle for the formulators today.

Sulfonamide is an important chemical class of synthetic active pharmaceutical ingredients. The class includes several groups of drugs used in the treatment of bacterial infections, diabetes mellitus, oedema, hypertension, and gout. Many sulfonamide APIs are classified as BCS class II and class IV drugs having low solubility issues and also have other stability issues such as hydration and polymorphic transformation etc. Modification and enhancement of physicochemical properties of the potential sulfonamide APIs which eventually permit

development of formulations with good solubility, dispersibility, stability, manufacturability, and patient compliance is need of the hour.

Due to the increased demand, there is no alternative than mass production of the solid-state analogs of sulfonamide APIs. Solvent-based crystallization methods often have low yield, low atom economy, large carbon foot prints and require large volumes of the solvents. This can contribute to generation of hazardous waste in the form of crystallization mother liquor. It possesses a need of an eco-friendly green methods for synthesis of solid-state sulfonamide analogs with enhanced physicochemical properties.

9. Research Methodology

- Selection of sulfonamide APIs: Selection of potential sulfonamide API belonging to BCS Class II or IV and identification of problem related to its application, use or synthesis methods.

- Systematic literature search: Literature search for reported strategies used to overcome selected problem, similar molecules having similar problem and their reported solutions, synthesis methods reported in literature for solid state analogs, green synthesis methods reported in literature and criteria for assessment of enhancement of selected physicochemical properties.

- Proximate analysis: Selected sulfonamide API, before being taken for processing, if not analysed can lead to changes in their original characteristics. To avoid this, sulfonamide API will be ascertained by tests like % purity, initial PXRD, Melting Point, solubility, thermal stability etc.

- Designing of solid-state analog for solution of issue: Proposed strategies to overcome the problem like development of new polymorph, solution by combination (Co-crystal/Eutectic mixtures), Development of novel solvate or hydrate with the help of green synthesis procedures.

- Experimentation: Synthesis of solid-state analogs: Screening of polymorph, Screening of co-crystals / Eutectic mixtures, Solvate / hydrate screening with the green methods

like solventless process, synthesis and crystallizations using green solvents, water assisted synthesis of solid-state analogs, etc.

- Characterization of solid-state analogs: Synthesized solid-state analogs will be characterized using various suitable analytical techniques like Powder X-ray Diffraction, Differential scanning calorimetry, Infra-red spectroscopy, Single crystal X-ray Diffraction, % w/w (in case of multi-component systems), % moisture content (in case of hydrates or water assisted synthesis) etc.

- Analysis of enhanced physicochemical properties: Analysis of enhanced physicochemical properties of sulfonamide analog synthesized by green procedure will be tested using suitable methods.

10. Statistical Plan

First Year	1. Selection of sulfonamide APIs and sample procurement 2. Literature search 3. Proximate analysis
Second Year	1. Designing of solid-state analog for solution of issue: Proposed strategies to overcome the problem 2. Experimental work: Screening of polymorph, Screening of co-crystals / Eutectic mixtures, Solvate/hydrate screening with green methods 3. Characterization of Solid-state analogs
Third Year	1. Analysis of enhanced physicochemical properties 2. Planning for national and international conference 3. Decision on intellectual property and publication of results (for results not essential for patenting)

11. Limitations of the study

Some of the Instruments required for the analysis purpose are not available in the college hence, it needs to be outsourced.

12. Expected Results and outcome

- Preparation of novel solid-state sulfonamide API analogs with the help of single component solid-state synthesis (polymorph screening) and multi component solid-state synthesis (co-crystals, solvates, eutectics, etc.) followed by their characterization (by PXRD, DSC, IR, Single Crystal XRD, % w/w (in case of multi-component systems), % moisture content (in case of the hydrates or water assisted synthesis) and other relevant spectroscopic methods to understand structure-property relationship.
- Novel green eco-friendly methods for synthesis of solid-state sulfonamide API having low waste generation, low carbon foot print, minimal solvent usage, high selectivity, high atom economy.
- The effort will lead to provide novel solutions through solid-state sulfonamide analogs with enhanced properties synthesized by the green methods.
- Improved understanding of the strategies for molecular modifications that can be used to design and develop solid-state APIs with the desired properties

13. Select Bibliography

[1] M. A. Neumann, J. van de Streek, F. P. A. Fabbiani, P. Hidber, O. Grassmann, Nature Commun., 6:7793,1-7 (2015).

[2] J. Dunitz and J. Bernstein, Acc. Chem. Res., 28, 193-200 (1995).

[3] K.P.Kadam, R.P.Chavan, IJES, 5:6, 29-34 (2016).

[4] S. S. Kumar, S. Rana and A. Nangia Chem. Asian J., 8, 1551-1571(2013).

[5] G. Nithya, Sudha R., C. Kanakam, Asian Journal of Pharmaceutical and Clinical Research 10:4, 259-262 (2017).

[6] M. Briones, G. Dotor, J. Franco, Pharmaceutics., 13:6, 790-838 (2021).

[7] V. Lopez-Mejías and A. J. Matzger, Cryst. Growth Des., 15:8, 3955-3962 (2015).

[8] N. Blagden, M. de Matas, P. T. Gavan, York, P. Adv. Drug Deliv. Rev., 59:7, 617-630 (2017).

[9] M. K. Nazeeruddin, A. Kay, I. Rodicio, R. Humphry-Baker, E. Muller, P. Liska, N. Vlachopoulos, M. Gr_tzel, J. Am. Chem. Soc., 115:14, 6382-6390 (1993).

[10] C.-H. Zhao, A. Wakamiya, Y. Inukai, S. Yamaguchi, J. Am. Chem. Soc., 128:50, 15934-15935 (2006).

[11] B.-K. An, S. H. Gihm, J. W. Chung, C. R. Park, S.-K. Kwon, S. Y. Park, J. Am. Chem. Soc., 131:11, 3950-3957(2009).

[12] P. Sanphui, B. Sarma, and A. Nangia, Cryst. Growth Des., 10:10, 4550–4564 (2010).

[13] M. Banik, S. Prasad, S. Ganguly, and G. R. Desiraju, Cryst. Growth Des., 16:9, 5418–5428 (2016).

[14] G. Bolla, S. Mittapalli, A. Nangia, Cryst. Eng. Comm., 16, 24-27 (2014).

[15] J. Bernstein, Crystal Growth & Design, 2:6, 675–676 (2002).

[16] T. Mutai, H. Tomoda, T. Ohkawa, Y. Yabe, K. Araki, Angew. Chem. Int. Ed., 47:49, 9522-9524 (2008).

[17] S. R. Chemburkar, J. Bauer, K. Deming, H. Spiwek, K. Patel, J. Morris, R. Henry, S. Spanton, W. Dziki, W. Porter, J. Quick, P. Bauer, J. Donaubauer, B. A. Narayanan, M. Soldani, D. Riley, K. McFarland, Org. Proc. Res. Dev., 4:5, 413-417 (2000).

[18] F. Rodriguez-Caabeiro, A. Criado-Fornelio, A. Jimenez-Gonzalez, L. Guzman, A. Igual, A. Perez, M. Pujol, Chemotherapy, 33:4, 266-271(1987).

[19] S. S. Yang, J. K. Guillory, J Pharm Sci.,61:1, 26-40 (1972).

[20] F.Blasco, L.Perellóa, J.Latorre, J.Borrása, S.Garciá-Granda, J. In. Bio, 96, 143-154 (1996).

[21] J.M. Leger, S. Alberola et A. Carpy, Acta Cryst., B33, 1455-1459 (1977).

[22] S. A. Ross, D. A. Lamprou ORCID logo, D. Douroumis, Chem. Commun., 52, 8772-8786 (2016).

[23] F. Luis, F. Soares, and R. Lajarim, Cryst. Growth Des., 13:4, 1510–1517 (2013).

[24] V. López-Mejías, J. Kampf, A. Matzger, J. Am. Chem. Soc, 134:24, 9872-9875 (2012).

[25] Lindenberg M., Kopp S., Dressman J. B. Eur. J. Pharm. Biopharm., 58, 265–278 (2004).

[26] A. N. Kasim, M. Whitehouse, C. Ramachandran, M. Bermejo M., H. Lennernas, A. Hussain, E. H. Junginger, A. S. Stavchansky, K. K. Midha, P. V. Shah, L. G. Amidon, Mol. Pharm., 1, 85–96 (2004).

[27] T. Takagi, C. Ramachandran, M. Bermejo, S. Yamashita, Yu L. X., L. G. Amidon, Mol Pharm., 3, 631–643 (2006).